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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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ROPES & GRAY
ONE INTERNATIONAL PLACE
BOSTON, MA 02110-2624

EXAMINER
BRANNOCK, MICHAEL T

ART UNIT	PAPER NUMBER
1646	16

DATE MAILED: 01/28/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/451,939	Miao, et al.
Examiner	**Art Unit**
Michael Brannock, Ph.D.	1646

-- The MAILING DATE of this communication appears on the cover sh et with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Nov 19, 2001*

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-51* is/are pending in the applica

4a) Of the above, claim(s) *13-15, 17-21, and 23-51* is/are withdrawn from considera

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-12, 16, and 22* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirem

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

Status of Application: Claims and Amendments

1. Applicant is notified that the amendments put forth in Paper 15, 11/19/01, have been entered in full.

2. Claims 1-51 are pending

3. Claims 13-15, 17-21, 23-48 and new claims 49-51 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim, as set forth previously in Paper 12, 7/17/01 Further, Applicant is reminded that claims 1-12, 16 and 22 will be examined only to the extent that the claims read on the invention of elected Group II , i.e. *in vivo* administration of the elected species: small molecule agonists or antagonist of patched that are not Protein Kinase A inhibitors, as also set forth in Paper 12.

Withdrawn Rejections:

4. The rejection of claims 5-12 and 22 under 35 U.S.C. § 101, as set forth in item 2 of Paper 12 is withdrawn in view of Applicant's amendments in Paper 15.

5. The rejection of claims 1-12, 16, 22 under 35 U.S.C. 112, second paragraph, as set forth in item 4 of Paper 12 is withdrawn in view of Applicant's amendments in Paper 15.

Maintained rejections:

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-12, 16, and 22 stand rejected under 35 U.S.C. 112, first paragraph, as set forth in item 6 of Paper 12, because the specification, while being enabling for a method of promoting the survival of Dopamine and GABA neurons *in vitro* or in embryonic tissue explants comprising contacting the neurons with sonic hedgehog, does not reasonably provide enablement for *in vivo* methods of promoting the survival of dopaminergic or GABAergic cells comprising the administration of a small molecule agonist or antagonist of patched that is not Protein Kinase a inhibitor nor treatment of diseases in the adult animal with any ptc therapeutic. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicant argues that Applicant's have provided extensive evidence that patched therapeutics promote neuronal survival. Specifically, Applicant appears to argue that Applicant's *in vitro* data with embryonic mesencephalon explants would lead one of skill in the art to extrapolate the data to any other neural tissue (see first full paragraph of page 8 of Paper 12). This argument has been fully considered but not deemed persuasive. One of skill in the art

appreciates that the nervous system, particularly the human nervous system, is perhaps the most complex system in the known universe. The development and regulation of which are under the control of finely tuned and complex mechanisms that are extraordinarily specific, both during the temporal course of development and in the specificity of particular interactions between specific neuronal cell types and the multitude of factors, such as hedgehog, that control them - as is well established in the art. Therefore, one of skill in the art would not reasonably conclude that it is more likely than not that a factor such as sonic hedgehog, which is known only to influence the developmental course of certain neuronal populations in the embryo, would have similar properties on other neuronal types or in the adult wherein development has stopped.

Applicant asserts that immunophilin ligands and a neurotrophin family member (GDNF) and have been shown to protect both embryonic and adult nerve cells from that MPP+ toxicity and because sonic hedgehog has been shown to protect embryonic nerve cells, then it is more likely than not sonic hedgehog would also protect adult nerve cells (see second full paragraph of page 8-9 of Paper 12). This argument has been fully considered but not deemed persuasive. It is well known that immunophilin ligands and neurotrophin family members are completely unrelated, structurally and functionally, to hedgehog proteins. Further, neurotrophins are known to be important both during development and in the adult as trophic factors for neurons - as is well established in the art. Similarly, immunophilin ligands are well known to be active in the adult, where as hedgehog is not. Thus, one of skill in the art would not expect that it is more

likely than not that the effects of hedgehog in the adult would be similar to either immunophilin ligands or GDNF.

Applicant argues that the specification provides adequate guidance as to how to identify small molecule hedgehog agonists, that are not PKA inhibitors, as exemplified by the post-filing date published PCT Application WO 01/74344. Applicant argues that the specification teaches the use of a high through-put screen for the identification of such molecules. This argument has been fully considered but not deemed persuasive because it is obvious to one skilled in the art that the identification of the hedgehog agonists of the PCT Application WO 01/74344 is the result of extensive research and investigation by the authors of that Application. The instant specification provides to the skilled artisan only an invitation to perform research and investigation to try and find non-PKA-inhibitors that are agonists of hedgehog. No specific structural information, regarding the supposed agonists, to use to begin a high through-put screen has been given. Only the desired function and assays to measure the function of the agonist are taught in the specification. However, as the skilled artisan readily appreciates, a simple wish for a compound with a particular function is not adequate guidance to produce that compound.

Applicant argues that Stull and Iacovitti, cited by the examiner, is not applicable to the present invention, primarily because none of the experiments of Stull and Iacovitti examine the effects of Shh administration in the absence of FGFs. This argument has been fully considered but not deemed persuasive. Applicant's attention is drawn to page 39, first paragraph of

RESULTS, wherein Stull and Iacovitti and discuss the results of experiments wherein Shh alone or in combination with FGF is added to the explants.

In summary Applicant argues that the specification provides ample *in vitro* evidence that activation of hedgehog signaling increases neuronal survival. The examiner contends that the evidence is sufficient to predict the effects of sonic hedgehog, *in vivo*, on an embryo, because of the known involvement of hedgehog in the embryo. However, because of the known lack of involvement of hedgehog in the adult, one would not expect to extrapolate the effects of hedgehog from Applicant's *in vitro* data on embryonic tissue to what the effect might be *in vivo* on adult tissue.

Further, Applicant Argues induction of gene expression indicative of hedgehog signaling would lead one of skill in the art to reasonably conclude that other agents that stimulate hedgehog signaling would have a similar effect on neuronal survival. This argument has been fully considered but not deemed persuasive. The effects of hedgehog signaling are extremely complex. Applicant has not established what particular aspect of hedgehog signaling produces increases in survival of embryonic explant neurons. While it is true that one would expect that agents that directly promote the binding of hedghog to patched or directly mimic the effect of that binding would be expected to increase neuronal survival in embryonic explants, the issue is that no such compounds have been put forth in the specification, and nor has the specification provided sufficient guidance to attain them.

Finally, Applicant argues that strong *in vitro* evidence can reasonably be correlated with *in vivo* situations. This point has not been contested; the issue is that while the specification has sufficient *in vitro* evidence to provide a correlation between *in vitro* and *in vivo* embryonic tissue, the claims encompass modulating adult tissue and there are no *in vitro* data concerning adult tissue in which to make a correlation.

8. Claims 1-12, 16 and 22 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, as set forth previously in item 7 of Paper 12.

The claims require *in vivo* methods of promoting the survival of dopaminergic or GABAergic cells comprising the administration of a small molecule hedgehog agonist that is not Protein Kinase A inhibitor. However, there appears to be no description of such a molecule, nor guidance as to what structural characteristics such a molecule might possess, nor is such a molecule known in the art.

Applicant argues that the specification has provided ample guidance to allow one skilled in the art to envision the characteristics of the small molecules of the invention. Applicant appears to base this argument on the fact that the specification outlines the functional properties that the molecules should have. This argument has been fully considered but not deemed persuasive because these hypothetical functional properties tell the skilled artisan absolutely

nothing about the identity of the claimed compounds. Applicant further argues that the specification provides assays for identifying the claimed compounds. This argument has been fully considered but not deemed persuasive. The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art. This problem may arise where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art recognized correlation or relationship between the structure of the invention and its function (see Fed Res. Vol. 66, No. 4, January 5, 2001, page 1105, col 1, A.). In the instant case, the specification has presented only an invitation to the skilled artisan to try to find a compound with the function of being a small molecule hedgehog agonist that is not Protein Kinase A inhibitor and there is no art-recognized correlation between this recited function and any structure because there are no known molecules having theses characteristics.

Thus the specification provides simply an invitation to try to find a molecule having the recited properties and say nothing about the actual identity of any compound, such that one skilled in the art would recognize that Applicant was in possession of the compound at the time the application was filed.

9. Claims 1-3 stand rejected under 35 U.S.C. 102(b) as being anticipated by *Hynes et al. Neuron* 15(1)35-44, 1995, as set forth in item 9 of Paper 12.

Hynes et al. disclose a method of promoting the survival of midbrain neurons, e.g. substantia nigra dopaminergic and GABAnergic neurons comprising contacting the cells with a trophic amount of sonic hedgehog protein, i.e. a hedgehog agonist (see the Abstract).

Applicant argues that Hynes et al. do not address a post-inductive role for sonic hedgehog and therefore due not anticipate the claims. This argument has been fully considered but not deemed persuasive. Applicant is reminded that the claims do not require a post-inductive role. Never-the-less, Hynes et al. teach the administration of sonic hedgehog to embryonic midbrain neurons past the point of induction of tyrosine hydroxylase (TH) activity which is known to be about E12.5, see page 36, RESULTS. Hynes et al. cultured the E9 explants for 5 days in the presence of sonic hedgehog and then measured the presence of TH neurons (page 37). Thus, the endpoint of the assay is the survival of midbrain TH positive cells e.g. substantia nigral dopaminergic and GABAnergic neurons - as a function of Shh concentration, post induction (see Fig. 4). Although Hynes et al. was particularly interested in the inductive effect of Shh, the survival promoting effect of hedgehog on TH neurons cannot logically be divorced from the inductive effect because it is the survival of these neurons that is the measured end-point of the assay. Thus, Applicant is not correct in the assertion that the experiments do not or cannot address the role of hedgehog signaling in promoting cell survival, because it is cell survival that has, in fact, been measured as a function of hedgehog signaling.

Conclusion

10. No claims are allowable.

11. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Brannock, Ph.D., whose telephone number is (703) 306-5876. The examiner can normally be reached on Mondays through Thursdays from 8:00 a.m. to 5:30 p.m. The examiner can also normally be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, Ph.D., can be reached at (703) 308-6564.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

MB

January 25, 2002

YVONNE EYLER, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600